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Reagent-free synthesis of 2,3,4-polysubstituted tetrahydroquinolines: application to the formal synthesis of (±)-martinellic acid and martinelline

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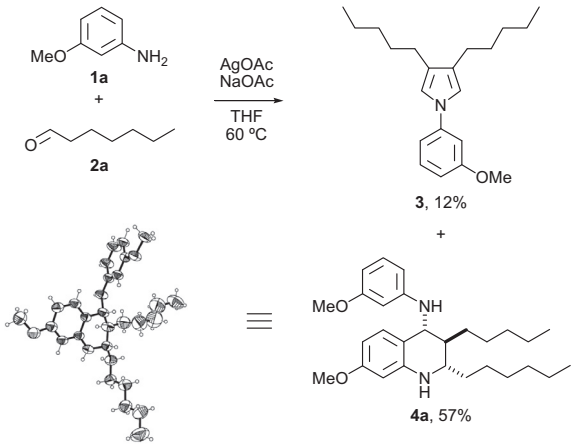
ABSTRACT

The simple and one-pot method for the synthesis of polysubstituted tetrahydroquinolines from readily available anilines and aldehydes under reagent-free conditions has been developed. The scope of the transformation has been demonstrated. This method has been successfully applied to the rapid formal synthesis of (±)-martinellic acid and martinelline.

The tetrahydroquinoline (THQ) nucleus is one of the most important heterocycles. It is commonly found in many natural products and synthesized bioactive molecules. A variety of methods have been developed to construct THQs and their derivatives.[1] Among them, the imino Diels–Alder reaction (Povarov reaction) between *N*-arylimines and nucleophilic olefins is probably one of the most powerful synthetic tools, since it is convenient for the synthesis of 1,2,3,4-tetrahydroquinolines bearing complex substituents at C-2, C-3, and/or C-4 of the heterocyclic ring.[2] However, Brønsted or Lewis acids have to be used as catalysts in most cases. Very few examples of preparing polysubstituted THQs without any use of acids have been reported, albeit in low yield or low stereoselectivity.[3] Herein, we report a simple and efficient one-pot approach to the preparation of 2,3,4-polysubstituted THQs from readily available anilines and aldehydes under reagent-free conditions. The method was successfully applied to the formal synthesis of (±)-martinellic acid and martinelline.

During the course of our synthesis of polysubstituted pyrroles using AgOAc as the oxidant,[4] we unexpectedly discovered that when *m*-anisidine (**1a**) and heptanal (**2a**) were used as the reactants, the desired pyrrole **3** was obtained in only 12% yield; instead, the THQ **4a** was obtained in 57% yield, which was unambiguously confirmed by X-ray crystallographic analysis (Scheme 1).[5] The formation of tetrahydroquinoline **4a** could be explained as illustrated in Scheme 2. Reaction of *m*-anisidine (**1a**) with heptanal (**2a**) rapidly produces imine **A**, which might equilibrate to enamine **B**. Imine **A** is attacked by emamine **B** to afford the imine **C**.[6] Finally, the imine **C** reacts with the intramolecular aromatic ring of aniline to provide the so-obtained THQ **4a**.

Theoretically, neither oxidants nor bases are needed for the formation of **4a**. Therefore, the reaction conditions were further



Scheme 1. The unexpected formation of THQ **4a**.

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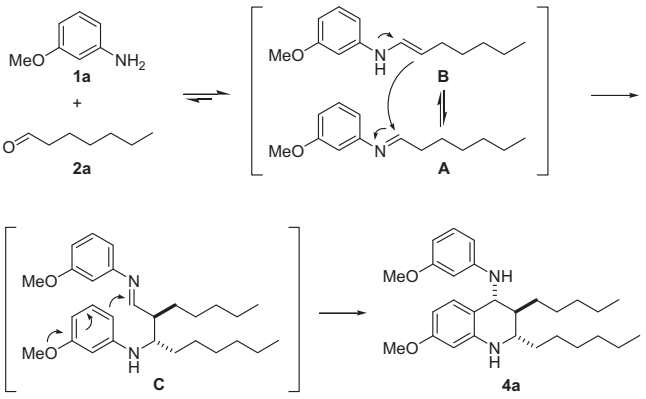


Scheme 2. Proposed mechanism for the formation of THQ **4a**.

optimized using *m*-anisidine (**1a**) and heptanal (**2a**) as starting materials. Finally, we found when the reaction was carried out in THF at 60 °C without any other reagents, the THQ **4a** could be obtained in 90% yield. It is also noteworthy that these transformations were highly stereoselective and only the 2,3-trans-3,4-trans diastereomers were obtained. The advantage of the high yield and high stereoselectivity, as well as reagent-free conditions promoted us to study this reaction.

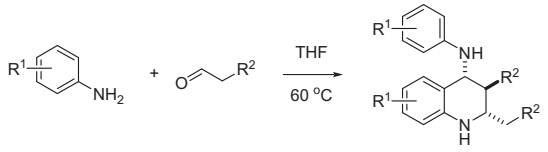
Having established the optimal reaction conditions, the scope of this reaction was examined with respect to the aldehydes and amines. As illustrated in Table 1, some readily available aldehydes were chosen to react with *m*-anisidine (**1a**). The reaction was found to be very general and a diverse set of aldehydes were suitable reaction partners, affording the corresponding THQs in excellent yields (**4a**–**4f**). The adipaldehyde was also tested and the reaction gave the desired product **4g**, albeit in 24% yield (Table 1). Compound **4g** was unambiguously confirmed by X-ray crystallographic analysis.[5]

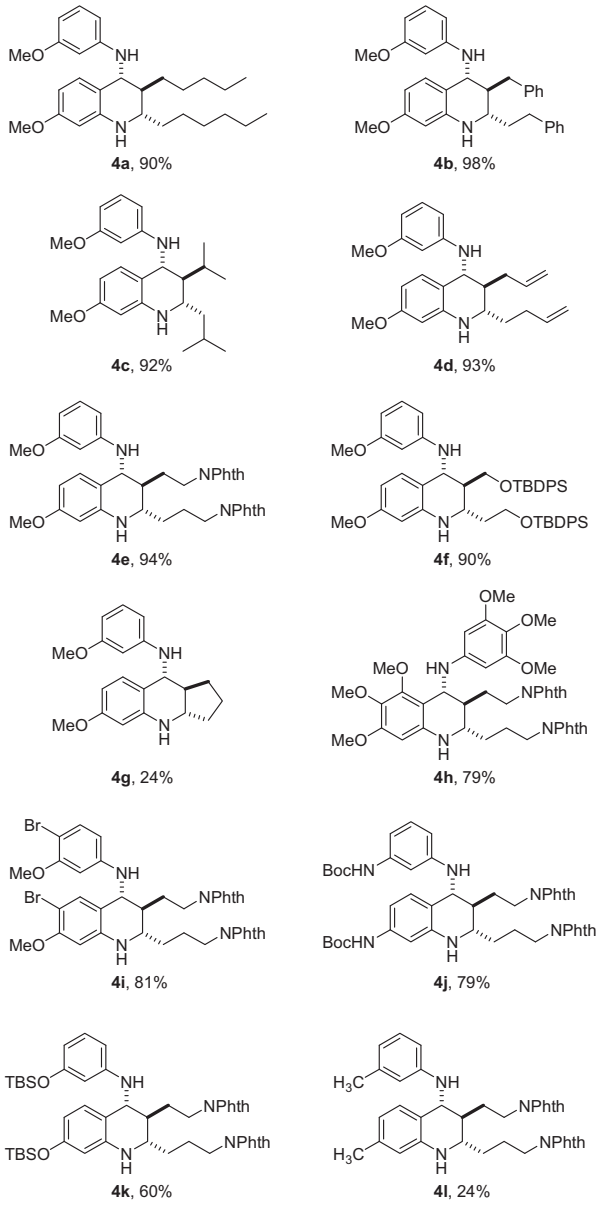
To investigate the reactivity of amines, some anilines were chosen to react with 4-(1,3-dioxoisoindolin-2-yl)butanal. The desired THQs **4h**–**4k** were obtained in moderate to good yields. It is noteworthy that halosubstituted anilines survived the reaction conditions and formed the halo-substituted THQs **4i**, which could be used for further transformations. The THQ **4l** was obtained in only 24% yield while anilines without the electron-donating groups (EDGs) in the *meta* positions could not produce the corresponding THQs under our standard conditions. These results indicated that the EDG in *meta* position of the aniline is essential for this transformation since it enhances the nucleophilicity of the aromatic ring, which is illustrated in Scheme 2.

This method was also suitable for scale up. For example, THQs **4b** was prepared in 10 g scale without decreasing the yield.

The utility of this method was demonstrated by a concise formal synthesis of (±)-martinelline (**5**) and martinellic acid (**6**) (Fig. 1),[7] novel non-peptide antagonists for the bradykinin (BK) B_1 and B_2 receptors.[8–11] Our synthesis commenced with THQ **4j** (Scheme 3). Treatment of THQ **4j** with N-bromosuccinimide gave dibromo THQ **7** in 80% yield. Deprotection of the two *N*-Phth groups using hydrazine hydrate followed by treatment with 1 N HCl gave the tricyclic skeleton of (±)-martinellic acid **9**, which was then protected with trifluoroacetic anhydride to provide the amide **10** in 42% overall yield. Deprotection of the *N*-Boc group using trifluoroacetic acid, followed by the reductive removal of the amino group via diazonium intermediate smoothly gave compound **11** in 76% overall yield. Carbonylation[8e,9a] of **11** under optimized conditions gave ester **12** in 98% yield. Our formal synthesis was completed by the cleavage of the TFA group using HCl/MeOH, which gave Ma's intermediate **13**, whose physical properties (^{1}H, and ^{13}C NMR, MS data) were in accordance with those described in the literature.[8a,e] Thus, our synthesis of Ma's intermediate was achieved in seven steps and 20% overall yield from **1j**.

Table 1
Substrate scope of the preparation of tetrahydroquinolines from anilines and aldehyde





Reaction conditions: **1** (1 mmol), **2** (1 mmol), THF (4 mL), 60 °C, 10 h. All the yields are isolated yields. Phth = phthaloyl; TBDPS = *tert*-butyldiphenylsilyl.

In summary, we have developed a simple and efficient method for the synthesis of 2,3,4-polysubstituted tetrahydroquinolines from readily available anilines and aldehydes under reagent-free conditions. The scope of the transformation was studied and its utility was demonstrated by the rapid formal synthesis of (±)-mar-

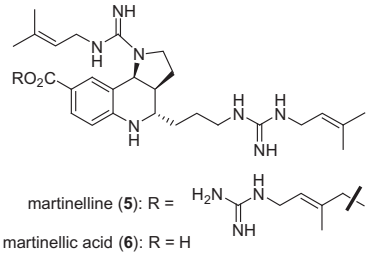
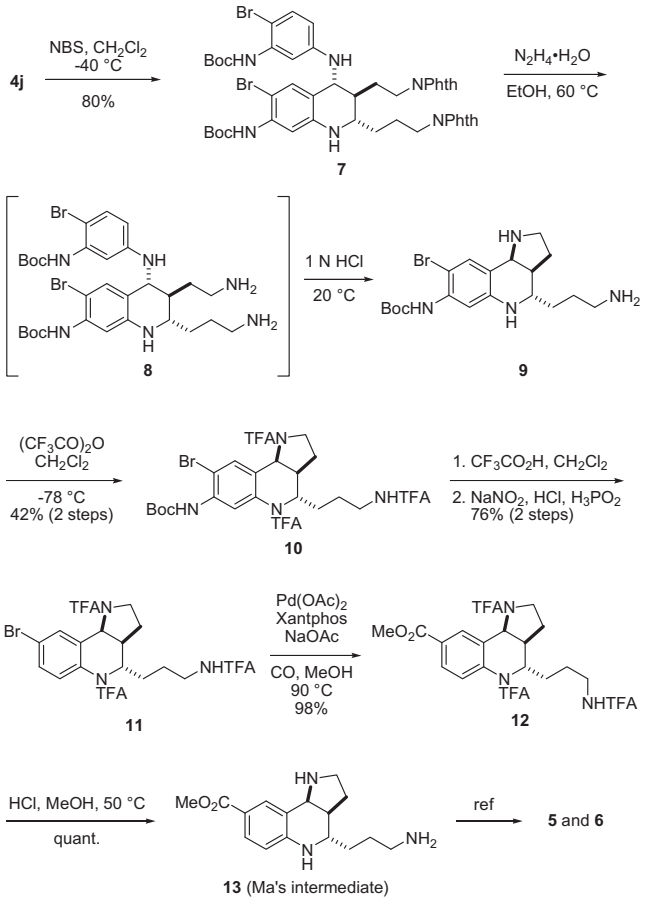


Figure 1. Structures of martinelline and martinellic acid.



Scheme 3. Formal synthesis of (±)-martinellic acid and martinelline.

tinellic acid and martinelline, which was achieved with a much shorter route.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.028.

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